PATENT COOPERATION TREAT

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
P3195PC00		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2007/058438	15/08/2007	16/08/2006
Applicant		
ACTION MEDICINES, S.L.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [X] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [X] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/058438

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/192 A61K31/10 A61P17/00 A61K31/60 A61K31/618

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/029484 A (AJINOMOTO OMNICHEM S A [BE]; ESTEE LAUDER COORDINATION CT N [BE]; DECL) 23 March 2006 (2006-03-23)	1,2,5, 12,17
Y	page 13, paragraph 34 page 21, paragraph 44 claims 1,14	1-18

X	US 2005/175559 A1 (DINARDO JOSEPH C [US] ET AL) 11 August 2005 (2005-08-11)	1,2,6, 12,14, 15,17
	page 1, paragraphs 3,7 page 2, paragraph 24 page 3, paragraph 31 claim 1	

	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2007	27/11/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Damiani, Federica

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	US 2007/149618 A1 (CUEVAS SANCHEZ PEDRO [ES] ET AL) 28 June 2007 (2007-06-28) page 35, paragraph 3 claims 1-8	1,2,5, 8-10, 12-15,17
Y	US 6 281 203 B1 (TOUZAN PHILIPPE [FR] ET AL) 28 August 2001 (2001-08-28) column 1, line 25 - line 26 column 3, line 43 - line 51 column 4, line 6 column 5, line 14 - line 25	1-18
Y	WO 96/17589 A (KAO CORP [JP]; FUJIMURA TSUTOMU [JP]; OGAWA AYUMI [JP]; OHSU HIROYUKI) 13 June 1996 (1996-06-13) page 22; compound 20 page 29, last paragraph claim 1	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/058438

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17,18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/058438

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006029484 A	23-03-2006	AU 2004323347 A1	23-03-2006
		CA 2579784 A1	23-03-2006
		EP 1799228 A1	27-06-2007
US 2005175559 A1	11-08-2005	WO 2005077111 A2	25-08-2005
US 2007149618 A1	28-06-2007	NONE	
US 6281203 B1	28-08-2001	AT 220536 T	15-08-2002
		BR 9903434 A	26-09-2000
		CA 2279722 A1	17-02-2000
		CN 1245054 A	23-02-2000
		DE 69902131 D1	22-08-2002
		DE 69902131 T2	07-11-2002
		EP 0987011 A1	22-03-2000
		ES 2181376 T3	16-02-2003
		FR 2782269 A1	18-02-2000
		JP 3595206 B2	02-12-2004
		JP 2000063263 A	29-02-2000
		KR 20000017297 A	25-03-2000
WO 9617589 A	13-06-1996	NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2007/058438	15.08.2007	16.08.2006

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/192 A61K31/10 A61P17/00 A61K31/60 A61K31/618

Applicant
ACTION MEDICINES, S.L.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Damiani, Federica Telephone No. +49 89 2399-2664

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 17, 18 (IA)

because:

☒ the said international application, or the said claims Nos. 17, 18 (IA) relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,4,7-11,13,16,18
	No:	Claims	1,2,5,6,12,14,15,17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

1. The application relates the use of 2,5 dihydroxybenzene derivatives for the treatment of actinic keratosis.

Re Item III.

Claims 17, 18 are directed to a method of therapeutical treatment which is subject matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

2. Reference is made to the following document:
Unless otherwise indicated, reference is made to the passages indicated in the search report.

D1: WO 2006/029484 A (AJINOMOTO OMNICHEM S A [BE]; ESTEE LAUDER COORDINATION CT N [BE]; DECL) 23 March 2006 (2006-03-23)

D2: US 2005/175559 A1 (DINARDO JOSEPH C [US] ET AL) 11 August 2005 (2005-08-11)

D3: US 2007/149618 A1 (CUEVAS SANCHEZ PEDRO [ES] ET AL) 28 June 2007 (2007-06-28)

D4: US-B1-6 281 203 (TOUZAN PHILIPPE [FR] ET AL) 28 August 2001 (2001-08-28)

D5: WO 96/17589 A (KAO CORP [JP]; FUJIMURA TSUTOMU [JP]; OGAWA AYUMI [JP]; OHSU HIROYUKI) 13 June 1996 (1996-06-13)

D3 was published after the claimed priority; on the presumption that the priority is valid, this document is not taken in account as prior art for the purpose of the present opinion.

3. NOVELTY

D1 discloses the use of compounds of formula (I) (gentisic acid and homogentisic acid) for the treatment i.a. of photoinduced keratoses; accordingly, claims 1,2,5,12,17

are not new (Article 33(2) PCT).
D2 discloses the use of a compound of formula (I) to reduce skin hyperpigmentation comprising also increased pigment due to actinic keratosis. Accordingly, claims 1, 2, 6,12,14,15,17 are not new (Article 33(2) PCT).

4. INVENTIVE STEP
In as far as the subject matter is new, the following observations to the requirement of inventive step apply.
D1, D2 relating to the use of compounds of formula (I) for the treatment of actinic keratosis can be regarded as the closest prior art. Only minor modifications to the compounds disclosed in D1, D2 if any, are required in order to arrive to the new claimed derivatives. Such minor modifications must therefore be regarded as obvious solution to the provision of alternative compounds for the treatment of actinic keratosis. Accordingly, an inventive step can not be acknowledged in the absence of evidence showing that substantially all the claimed compounds have unexpected property or improved activity with respect to the structurally closest prior art compounds.
In addition, D4 and D5 describe further compounds of formula (I) as keratolytic agents for the treatment of signs of skin ageing in particular caused by photoageing. Therefore, it would be obvious for the skilled person to use also the compounds of D4, D5 for the treatment of the related actinic keratosis.

5. FURTHER OBSERVATIONS

5.1 It is not evident what further compounds structures could actually be comprised by the additional definition of "prodrugs".

5.2 Claim 18 erroneously depends from claim 17 as it refers to a use whereas claim 17 refers to a method.

Re Item VI

Certain documents cited

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2007/058438

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
US20070149618	28.06.2007	16.08.2007	17.02.2004

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

PARTNERS
Juan Arias
M. Sc. Chemistry
European Patent Attorney
Spanish Patent & Trademark Agent
Francisco Bernardo
M. Sc. Chemistry
European Patent Attorney, CEIPI
Vicente González
M. Sc. Chemistry & Biotechnology
Spanish Patent & Trademark Agent
Fernando Prieto
B. Sc. Electronic Engineering, ICAI
Enric Carbonell
M. Sc. Chemistry
European Patent Attorney

ASSOCIATES
Agustín Alconada
Ph. D. Pharmacy (Molecular Biology)
Christine Weimann
Attorney-at-Law
Spanish Patent & Trademark Agent
Community Trademark & Design Attorney

ADVISERS
Cristina Zabalo
M. Sc. Chemistry
Almudena Fernández
Ph. D. Chemistry
Miguel Lorca
M. Sc. Chemistry
María García
Ph. D. Chemistry
Tomás Llamas
Ph. D. Chemistry
Esther Martínez
M. Sc. Biology
María José Carrascosa
Ph. D. Biology
Laura de la Vega
Ph. D. Physics
Ana Berlinches
Attorney-at-Law

FORMALITIES
Cecilia Ranilla
M. Sc. Business Administration
Spanish Patent & Trademark Agent

abg patentes

Madrid
Avenida de Burgos, 16 D
Edificio Euromor
E-28036 Madrid (Spain)
Tel: +34 91 417 13 00
Fax: +34 91 417 13 01

Barcelona
Comte d'Urgell, 143
E-08036 Barcelona (Spain)
Tel: + 34 93 452 59 58
Fax: + 34 91 417 13 01

abg
patentes
ARIAS , BERNARDO & GONZÁLEZ
Asesoría y Agencia de la Propiedad Industrial
Intellectual Property

EUROPEAN PATENT OFFICE
Erhardtstrasse, 27
D- 80331 – MÜNCHEN
Germany

CHAPTER II

Att.: International Preliminary Examination Authority

Only by fax

Our ref.: **P3195PC00**
Application No.: **PCT/EP2007/058438**

Madrid, July 17, 2008

Re: International PCT Application No. PCT/EP2007/058438 with title "USE OF 2,5-DIHYDROXYBENZENE DERIVATIVES FOR TREATING ACTINIC KERATOSIS", in the name of ACTION MEDICINES, S.L.
Reply to the written opinion (R 66.3 PCT) *[af]*

Dear Sirs,

We refer to our letter dated 12.06.2008 filing the Demand for Preliminary Examination of the reference application.

In reply to the Written Opinion issued under Rule 43bis.1 PCT, the applicant now files arguments supporting the patentability of the claims. They should be taken into account for the elaboration of the International Preliminary Examination Report.

Novelty

According to the opinion of the Examiner, claims 1, 2, 5, 12 and 17 of the present invention are not novel over D1 since this document describes the use of two particular compounds falling within the formula (I) for the treatment of photoinduced keratoses. However, we respectfully disagree with this opinion since D1 does not implicitly nor explicitly mention the specific use of gentisic or homogentisic acid in their respective phosphorylated forms to treat actinic keratoses. Rather, paragraph [0044] only mentions skin conditions resulting from aging, and among others, the term "keratoses" is disclosed. The term "keratoses" is a general term, rendering it unclear as to what particular conditions it refers. Moreover, the specific use of phosphorylated gentisic or homogentisic acid for the treatment of keratoses is not specifically disclosed among the different possible combinations of compounds and conditions which may be treated. On the other hand, the reference in claim 1 of D1 to the application of a topical composition to keratinous tissue does not mean that said tissue is affected by actinic keratoses. By keratinous tissue it is understood skin, hair and nails, i.e. tissues containing keratin [see abstract]. Therefore, it is neither derivable from claim 1 of D1 that

Consequently, claim 1 of the present application is novel over document D1. In addition, since claims 2, 5, 12 and 17 depend directly or indirectly on claim 1, we respectfully submit that said claims are also novel in view of D1.

Regarding D2, we also respectfully disagree with the opinion of the Examiner since this document does not specifically mention that the compound methyl gentisate, the only compound which falls within formula (I) of claim 1, could be used for treating actinic keratoses. Said compound is mentioned [par. 0031], among others, as an optional depigmenting agent to be incorporated in a formulation directed to the treatment of hyperpigmentation, wherein the active ingredient is an idebenone ester. As mentioned in the background of D2, hyperpigmentation is generally related to dense melanin concentration in skin tissues (melanocytes), whereas actinic keratoses involves the proliferation of keratinocytes. Keratinocytes constitute the epidermal epithelium and synthesize keratin, acting as the skin mechanical and permeability barrier, whereas melanocytes are scattered between keratinocytes of the epidermal basal stratum and they synthesize melanin which constitutes a protective barrier against non-ionizing ultraviolet light. Furthermore, pigmentation is not a common feature of actinic keratoses, whereas the pigmentation is almost always present for example in seborrheic keratoses.

Consequently, claim 1 is also novel over D2 and therefore all claims directly or indirectly dependent on it.

Inventive step

D1, considered by the Examiner as one of the possible closest prior art documents, describes the use of phosphorylated polyphenols for the treatment of a skin condition caused by skin aging or by photo- or environmentally-induced aging.

As mentioned above, claim 1 differs from D1 in that said document does not specifically mention the use of gentisic or homogentisic acid [compounds falling within formula (I) of claim 1] in their respective phosphorylated forms for the treatment of actinic keratoses.

The use of compounds of formula (I) has shown to be very efficient in the treatment of actinic keratoses as pointed out in examples 2, 3 and 4, wherein it has been demonstrated the *in vivo* significant reduction, or even the disappearance, of said condition in only a few weeks.

Therefore, the problem to be solved by the present invention can be seen as the provision of compounds which can efficiently treat actinic keratoses, particularly, in a short period of time.

The solution provided by claim 1 comprises the use of compounds of formula (I). This solution would not have been obvious for a skilled person in view of D1 since this document does not suggest that the specific compounds falling within the formula (I), i.e. gentisic and homogentisic acid in their phosphorylated forms, could lead to a significant reduction of the disease actinic keratoses in the affected area. D1 only relates to *in vitro* antioxidant results with resveratrol, a compound not encompassed by formula (I).

On the other hand, considering D2 as the closest prior art, claim 1 would differ from said document in that there is no specific disclosure of the use of methyl gentisate in the treatment of actinic keratoses as mentioned in the novelty analysis.

Therefore, the problem proposed by the present invention and the solution provided by claim 1 with respect to D2 can be considered the same as those mentioned for assessing the inventive step with respect to D1.

D2 neither suggests that the specific combination of a compound falling within formula (I), in this case methyl gentisate, could provide an efficient reduction of the disease actinic keratoses. Furthermore, in D2 said compound is included in the formulation for treating hyperpigmentation as an additional agent to the active ingredient, which acts as a depigmenting agent, but it is not derivable from D2 its use in the treatment of actinic keratoses. As mentioned in the novelty analysis, hyperpigmentation is generally related to dense melanin (melanocytes) concentration in skin tissues, whereas actinic keratoses involves the proliferation of keratinocytes.

Starting either from D1 or D2 and facing with the proposed problem, a skilled person would not have considered to combine any of these documents with D4 or D5 in order to solve the problem since said documents describe the use of compounds of formula (I) as keratolytic agents. The pathophysiological mechanism of actinic keratosis involves keratinocyte proliferation, altering the structure of epidermal tissue. Actinic keratoses is a pre-cancerous lesion more complex than an accumulation of skin keratin. Keratolytc agents, as mentioned in D4 and D5, act by eliminating keratin accumulation in the most superficial layer of the epidermis without affecting keratinocyte proliferation (a key event in actinic keratoses lesions). In fact, a well known keratolytic agent, glicolic acid (GA), has a poor efficacy in treating actinic keratoses lesions in patients when compared to an association with the anti-proliferative agent, 5-fluorouracil (5-FU), an approved drug for actinic keratoses treatment (19.67% vs 91.94% of efficacy for GA and GA+5-FU, respectively) (Marrero GM and Katz BE. *Dermatol Surg* 1998, 24:973-978).

Consequently, the use of compounds of formula (I) as defined in claim 1 for the treatment of actinic keratoses would not be obvious for the skilled person in view of the cited prior art. Since claims 2 to 18 depend directly or indirectly on claim 1, we respectfully submit that all claims are inventive over the cited prior art.

Thus, in view of the above comments and arguments, the applicant believes that the claimed invention meets the requirements of the PCT and thus, the issuance of a positive international preliminary examination report is respectfully requested. In case the IPEA intends to depart from said request, a telephone interview under R. 66.6 PCT (PCT Guidelines 19.31) is requested.

Very truly yours,

Juan Arias Sanz
European Patent Attorney
ABG Patentes, S.L.